American Journal of Medical Genetics 68:179–181 (1997)

Limb Anomalies in DiGeorge and CHARGE Syndromes

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Limb anomalies are not common in the DiGeorge or CHARGE syndromes. We describe limb anomalies in two children, one with DiGeorge and the other with CHARGE syndrome. Our first patient had a bifid left thumb, Tetralogy of Fallot, absent thymus, right facial palsy, and a reduced number of T-cells. A deletion of 22q11 was detected by fluorescence in situ hybridization (FISH). The second patient, with CHARGE syndrome, had asymmetric findings that included right fifth finger clinodactyly, camptodactyly, tibial hemimelia and dimpling, and severe club-foot. The expanded spectrum of the DiGeorge and CHARGE syndromes includes limb anomalies. Am. J. Med. Genet. 68:179–181, 1997

KEY WORDS: limb anomalies; CHARGE syndrome; DiGeorge syndrome; chromosome 22q11 deletion

INTRODUCTION

DiGeorge syndrome is comprised of conotruncal defects, immunodeficiency, endocrine abnormalities, and characteristic minor facial anomalies [Conley et al., 1979]. A deletion of 22q11 was found in a large number of patients [Driscoll et al., 1993]. The phenotypic spectrum is variable and recently rare limb anomalies such as preaxial polydactyly and club hands with hypoplastic metacarpals have been described [Cormier-Daire et al., 1995].

Ocular colobomas, congenital heart defects, choanal atresia, postnatal growth retardation, genital hypoplasia (including microphallus and cryptorchidism), and ear anomalies/or deafness [Pagon et al., 1981; Lubinsky, 1994] constitute the major diagnostic signs of CHARGE syndrome. Limb anomalies such as syndactyly and hypoplastic nails, although rare in CHARGE syndrome have been described [Meinecke et al., 1989; Siebert et al., 1985].

We describe two patients with these syndromes who have limb defects. Since limb anomalies are not usually considered part of the DiGeorge syndrome or CHARGE syndrome, we propose that their phenotypes be broadened to include limb defects.

CLINICAL REPORTS

Patient 1

This girl was born at term to non-consanguineous parents. Birth weight was 3,100 g (10th centile), length was 45 cm (5th centile), and head circumference (OFC) was 34.5 cm (50th centile). She had an asymmetric face with small ears, hypotelorism, a broad nasal bridge, a long philtrum, heart murmur, left bifid thumb, and mild hydronephrosis of the right kidney. No other skeletal anomalies were present.

An echocardiogram within hours of birth documented pulmonic stenosis and tetralogy of Fallot. During corrective surgery absence of thymus and right aortic arch were detected. Although T cells were moderately decreased in number, there was no evidence of T cell dysfunction She continues to have recurrent ear infections and has required two sets of ear tubes. Her speech is normal. She underwent surgical reconstruction of the bifid thumb at age 6 years. At 8 years she continues to be mildly hypotonic without major learning difficulties. Her IQ has been assessed in the average to low-average range.

Patient 2

This boy was born at 37 weeks of gestation to non-consanguineous parents. He weighed 2,700 g at birth (10th centile), was 46 cm long (3rd centile), and had an OFC of 32.5 cm (5th centile). Facial abnormalities included a hypoplastic lobe of the right ear (Fig. 1), right facial palsy, right choanal atresia with posterior choanal stenosis by CT scan, and bilateral coloboma of the iris and choroid (Fig. 2). In addition, right fifth finger clinodactyly and camptodactyly (Fig. 3), right tibial hemimelia, a tibial dimple and severe right club foot (Fig. 4), hypospadias, and a small left testis were present.

Examination of internal organs documented the presence of a patent ductus arteriosus, horseshoe kidney with hydronephrosis (left>right), severe gastro-esophageal

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Received 20 November 1995; Accepted 26 April 1996

Fig. 1. Small, posteriorly angulated ear in patient 2.

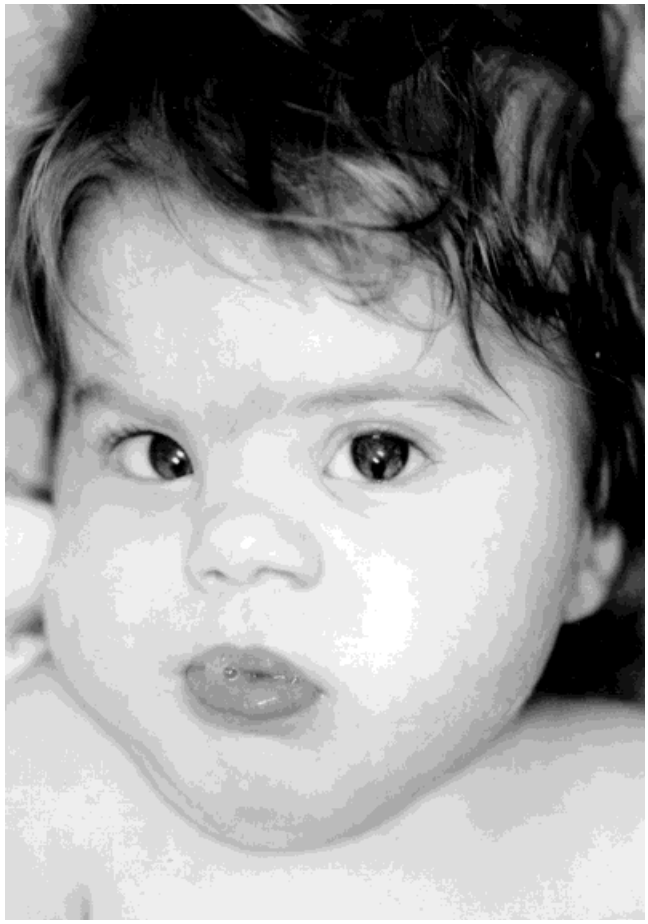

Fig. 2. Bilateral iris coloboma, epicanthal folds and asymmetric face of patient 2.

reflux, 11 pairs of ribs, and an aberrant right subclavian artery compressing the esophagus. Profound hearing loss was detected by brainstem evoked response audiometery. The proposed diagnosis was CHARGE syndrome, although the limb anomalies were unusual. The baby had tonic-clonic movements related to hypocalcemia (calcium of 6.6 mg/dl, normal 9.0–11.0 mg/dl; ionized calcium of 0.7 mg/dl, and normal 1.14–1.29 mg/dl), which resolved with calcium supplementation. At age 3 months, he is fed through a gastro-jejunal tube, has gained weight and is showing good head control.

CYTOGENETIC AND FISH INVESTIGATIONS

Karyotypes (550 band level) in both patients were normal. FISH (fluorescence in situ hybridization) studies were performed in both patients using a digoxigenin-labeled D22S75 probe for region 22q13.3. Patient 1 was found to have a chromosome 22q11 deletion which was not present in either parent. The other patient did not have the deletion.

DISCUSSION

Our first patient clearly had DiGeorge syndrome, confirmed by deletion of 22q11. Given this diagnosis, the presence of a left bifid thumb was an unexpected finding. Cormier-Daire et al. [1995], reported on two children with DiGeorge syndrome, one with preaxial polydactyly and one with club hands and hypoplastic metacarpal bones. Both had the 22q11 deletion. In 1993, Wilson et al., reviewed 44 children with DiGeorge syndrome and reported only one case with limb anomalies, a right "lobster claw" hand malformation. Thus, limb anomalies are uncommon in DiGeorge syndrome. Our second patient with CHARGE syndrome had limb malformations limited to the right side, including fifth finger clinodactyly, camptodactyly, tibial hemimelia, tibial dimple, and severe club foot.

In 1992, Emanuel et al. found evidence for 22q11 deletion in one of 18 patients with CHARGE "association." Furthermore, this deletion and CHARGE "association" have been described in one of the case reports by Clementi et al. [1991]. Their patient had a translocation of chromosomes 3 and 22, a deletion of the long arm of chromosome 22 and the CHARGE phenotype. Thus, there may also be overlap between the deletion 22q11 and CHARGE syndrome, particularly in the cardiac defects, immune defects, hypocalcemia and developmental anomalies. Ear and renal anomalies, along with mental retardation, are more frequently described in the CHARGE syndrome.

Fig. 3. Marked fifth digit camptodactyly in patient 2 (appears stiff with lack of PIP flexion crease and fixed DIP flexion).

We have searched for other reports of limb anomalies in children with CHARGE syndrome. Reported anomalies include cutaneous syndactyly [Siebert et al., 1985], nail hypoplasia of the second and third fingers on the right, and hypoplasia of the left second finger nail [Meinecke et al., 1989]. These findings are far less dramatic than those found in our patient. Recently atypical split hand/split foot deformity in two patients with CHARGE "association" were reported [Williams et al., 1996].

Genes located in the DiGeorge critical region have begun to be defined based on the characterization of a balanced translocation breakpoint in this syndrome [Budarf et al., 1995]. At least one gene, a novel putative adhesion receptor protein, was shown to be disrupted by this translocation. It was postulated that this gene product may play a role in neural crest cell migration. Based upon the size of the region deleted in DiGeorge and VCF syndromes and their variable phenotypes, there will likely be many more genes identified in this critical region that are important for the development of multiple cell lineages, including, possibly the limbs. Recent studies have advanced our understanding of the basic principles involved in limb development. For example, several genes in the HOX family, and fibroblast growth factors have been implicated during early limb morphogenesis [Tabin, 1995].

Fig. 4. Severe club foot deformity, tibial hemimelia, and dimpling in patient 2.

Our patient with CHARGE syndrome also had renal defects. Interestingly, in mice homozygous for mutant alleles of the limb deformity gene there is a marked reduction of the most distal structures of the limb and suppression of kidney development [Jackson-Grusby et al., 1992]. Further delineation of the genes involved in these genetic disorders of morphogenesis may aid in our understanding of the molecular defects causing limb anomalies.

Finally, we propose that limb anomalies, even minor ones, should be closely looked for when children are evaluated for DiGeorge or CHARGE syndromes.

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